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(19)(CA) **CANADIAN PATENT** (12)

(54) Formulations for Inhibiting Glucose Transport

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(73) Same as inventor

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NO DRAWING

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ABSTRACT

A formulation suitable for use for treating cancer, the formulation comprising:

(a) a glucose inhibiting (non-toxic) amount of an agent that blocks the glucose transport protein (active transport molecule in the membrane) of a cell from transporting glucose into the cell, and

(b) an effective (non-toxic) amount of an agent which

(i) enhances penetration and transport of agent (a) through the tissue surrounding the various cellular elements, generally known as scar tissue or fibrous reaction around the cancerous tumor, and

(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor.

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FIELD OF INVENTION

This invention relates to the treatment of cancer and particularly relates to new methods for the treatment of cancer, new formulations suitable for use in the treatment of cancer and the use of the new formulations in the treatment of cancer.

BACKGROUND OF THE INVENTION

Cancer cells require sugar (glucose) in order to survive. Under stressful conditions (for example hyperthermia, radiation and chemotherapy), the cancer cells require more sugar (glucose).

U.S. Patent 4,684,627 claims a method for the treatment of lung cancer which comprises administering lonidamine and one or more compounds selected from the group consisting of phlorizin, phlorizin glucoronide and 4-deoxy-phoretin-2-D-glucoside in an amount effective to inhibit glucose transport in the cancer cells while subjecting the cancer cells to additional therapy in the form of chemotherapy, thermal or radiation therapy.

U.S. Patent 3,523,937 purports to teach phlorizin analogues useful for eliminating glucose from humans and animals. In fact the patent states at column 1, line 58 that "the phlorizin analogues would be useful for any condition where the reduction of sugar is beneficial.

U.S. Patent 4,684,627 teaches that phlorizin "has now been found to be able to block glucose entry into cancer cells as well. The said patent further provides that "Cancer cells unlike normal cells require both glucose and oxygen to satisfy energy needs. The blocking of glucose entry impedes vital processes of the cancer cell and at elevated temperatures becomes lethal for cancer cells. By contrast, heat and the reduction of its glucose supply is well tolerated by normal tissues."

In tissue culture, the administration of the phlorizin, its glucoronide or 4d deoxyphloretin-2D glucoside can readily and

effectively inhibit glucose transport into cancer cells. Each one of these molecules effectively inhibit the growth of cancer cells in culture which can be demonstrated by decreased ^{14}C radioactive thymidine uptake. This effect is much greater on cancer cells compared to normal cells. Furthermore, the addition of other nutrients such as short chain fatty acids, restores the proliferation of normal cells but does not enhance proliferation of cancer cells in the presence of the molecules which block glucose transport.

In the large mammals such as the human, cancer cells grow in a group mass - tumors. When examined microscopically tumors consist of cellular elements with a vascular blood supply without smooth muscle present and a frequently dense collagen or fibrous tissue surrounding the various cellular elements, known as scar tissue or fibrous reaction around the tumor.

In the center of many tumors there is always partially necrotic or marginally viable cellular tissue since the tumor growth has "outstripped" its blood supply and is hypoxic, receiving insufficient oxygen.

While the teachings of U.S. Patent 4,684,627 (LeVeen) appear to suggest the use of compounds which inhibit glucose transport in the cancer cells to kill the cancer cells, in practice the results clearly are not the breakthrough being sought after. The reason may in part reside in the nature of the tumor itself - the scar tissue surrounding the various cellular elements and the necrotic or marginally viable cellular tissue at the center of many tumors. The compounds may not be able to penetrate into the center of tumor.

It is therefore an object of this invention to provide new methods for the treatment of cancer, new formulations suitable for use in the treatment of cancer and the use of the new formulations in the treatment of cancer.

Further and other objects of this invention will be realized by those skilled in the art from the following summary of the invention, embodiments of the invention and case studies.

SUMMARY OF THE INVENTION

According to one aspect of the invention, there is provided a new formulation suitable for use for treating cancer (for use in conjunction with at least thermotherapy (hyperthermia) and if desired, other modalities (such as chemotherapy or radiation)), the formulation comprising (for example in a pharmaceutically acceptable carrier):

(a) a glucose inhibiting (non-toxic) amount of an agent that blocks the glucose transport protein (active transport molecule in the membrane) of a cell from transporting glucose into the cell, and

(b) an effective (non-toxic) amount of an agent which

(i) enhances penetration and transport of agent (a) through the tissue surrounding the various cellular elements, generally known as scar tissue or fibrous reaction around the cancerous tumor, and

(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor.

According to another aspect of the invention, there is provided a combination formulation suitable for use for treating cancer, the combination comprising:

(a) a glucose inhibiting (non-toxic) amount of an agent that blocks the glucose transport protein (active transport molecule in the membrane) of a cell from transporting glucose into the cell, and

(b) an effective (non-toxic) amount of an agent which

(i) enhances penetration and transport of agent (a)

through the tissue surrounding the various cellular elements, generally known as scar tissue or fibrous reaction around the cancerous tumor, and

(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor.

After the introduction of the formulation or combination comprising agents (a) and (b) to the patient which have the effect of metabolically compromising the cancer cells of the tumor, the tumor and the cancer cells making up the tumor are stressed by at least thermotherapy (hyperthermia). In this regard, when agent (a) is transported into the tumor cells and the tumor cells are stressed, there is an inadequate amount of glucose available to the tumor cell for it to continue to function metabolically. Thus the tumor cell is impaired in its energy supply and dies. Therefore according to another aspect of the invention, a method for the treatment of cancer comprises administering (for example in a pharmaceutically acceptable carrier):

(a) a glucose inhibiting (non-toxic) amount of an agent that blocks the glucose transport protein (active transport molecule in the membrane) of a cell from transporting glucose into the cell, and

(b) an effective (non-toxic) amount of an agent which

(i) enhances penetration and transport of agent (a) through the tissue surrounding the various cellular elements, generally known as scar tissue or fibrous reaction around the cancerous tumor, and

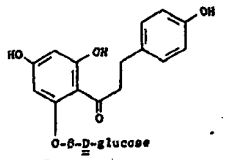
(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor,

and subjecting the cancer cells to hyperthermia (thermotherapy)

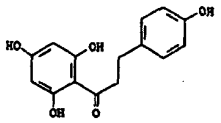
therapy. In some instances other modalities (for example chemotherapy and/or radiation therapy) may also be employed.

The glucose inhibiting (non-toxic) amount of an agent that blocks the glucose transport protein of a cell from transporting glucose into the cell (in cancer cells there appear to be more than in normal cells) may comprise:

Phlorizin



Phloretin



or their analogues including phlorizin glucoronide; 4-deoxy-phoretin-2-D-glucoside and the like.

The effective (non-toxic) amount of the agent which

(i) enhances penetration and transport of agent (a) through the tissue surrounding the various cellular elements, generally known as scar tissue or fibrous reaction around the cancerous tumor, and

(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor

may comprise dimethyl sulfoxide (DMSO), methylsulfonylmethane (MSM) (also called methylsulfone methane) or other carrier transport-type molecules having the characteristics which

(i) enhances penetration and transport of agent (a) through the tissue surrounding the various cellular elements, generally known as scar tissue or fibrous reaction around the

cancerous tumor, and

(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor.

With respect to the tissue cultures previously referred to to which one of the phlorizin, its glucoronide, and 4d-deoxyphloretin-2-D-glucoside were added, DMSO and MSM were added individually and the addition of DMSO or MSM (methylsulfone methane) enhanced the inhibition of cancer cell growth and allowed for a lower dose of the glucose blocking molecules (agent (a)). Because the cancer cell has a membrane which is less permeable than a normal cell it is believed the the carrier transport-type molecules such as DMSO and MSM enhance penetration of the glucose blocking molecules to the active transport molecule in the membrane. Preferred agents (a) are phlorizin and phloretin.

Irrespective of the agent however non-toxic amounts of the agents must be selected. Thus where amounts may be toxic, their introduction must be reduced to lower non-toxic levels over a prolonged period.

Phlorizin is preferably utilized at a dose of 70-350 mgm/kgm body weight given over a time period of 4-24 hours. If prepared without DMSO or MSM it may be given as solution of 10 gm phlorizin/litre of normal saline with 5 gm of sodium bicarbonate added to enhance solubility. DMSO is then administered. If phlorizin is used with DMSO it may be prepared using 500 ml normal saline, 2.5 gm sodium bicarbonate, 25 gm DMSO and 10 gms phlorizin. When utilizing MSM the preparation comprises 250 ml D/W5% (dextrose/water), 5 gm phlorizin, 20 gm MSM, and 1 gm sodium bicarbonate. When using non-alcohol based phlorizin, the preparation used may be 500 ml normal saline with 10 gm phlorizin. If using in combination with DMSO, 25 cc

may be added, or if adding MSM, 20 gm may be used per 500 ml bag.

Phloretin is preferably administered at a dose of 7-70 mgm/kgm body weight administered over 2-24 hours intravenously. Phloretin may be administered using a solution of 500 cc normal saline, 500 mg phloretin and 2.5 gm sodium bicarbonate. When used in combination with DMSO, the preparation may comprise of 500 cc normal saline, 1 gm phloretin, 2.5 gm sodium bicarbonate and 25 gm DMSO (100% solution). If using MSM rather than DMSO, the solution may comprise of 2 gm phloretin (250 ml D/W 5%) (dextrose/water), 1 gm sodium bicarbonate and 20 gm MSM.

Various cases are cited to illustrate the enhanced effect of tumor destruction produced clinically when agent (b) for example DMSO, MSM or other carrier transport-type molecules are administered in conjunction with agent (a), the molecules that block the glucose receptor, for example: phlorizin, phloretin, the glucoronide or phlorizin, etc:

CASE #1

A man with undifferentiated small cell carcinoma of the lung had metastasized to the liver. Neither the primary lung tumor nor the metastatic tumor in the liver showed more than a marginal response to chemotherapy by itself. The areas of the lung and the liver were treated with thermotherapy and phloretin was administered intravenously dissolved in bicarbonate and alcohol. This produced an effective response with complete regression of tumor in both instances demonstrating that there is activity of this glucose blocking molecule in conjunction with heat and chemotherapy. Subsequently the patient developed five metastatic tumors in the brain. These were treated with thermotherapy, chemotherapy and phloretin and showed a partial regression. When phloretin was dissolved in DMSO and

administered to the patient in combination with thermotherapy and a reduced dose of chemotherapy a marked and rapid regression was induced with all tumors disappearing within two weeks as demonstrated by computerized tomographic scanning.

CASE #2

A patient with carcinoma of the colon metastatic to the liver was treated for four sessions with combination of chemotherapy, thermotherapy and phloretin in a bicarbonate-alcohol solution. In addition the tumors were injected directly with alcohol. The patients tumors showed a partial response but without disappearance of all tumors. After one session of treatment with thermotherapy, chemotherapy, phloretin in DMSO there was complete regression of all tumors as demonstrated by sonographic assessment of the liver five weeks after treatment. The patients liver function tests had returned to normal and the circulating carcinoembryonic antigen had dropped substantially.

CASE #3

A female patient with a primary nonsecretory islet cell tumor of the pancreas metastatic to the lymph nodes and the liver was treated for three years with a combination of phloretin, chemotherapy and hyperthermia. The tumor remained stable and then in the past six months began to grow. She was treated with additional chemotherapy with some regression of the disease. Subsequently she was treated with one course with thermotherapy, chemotherapy and phloretin in 5% DMSO with a dramatic reduction in tumor size albeit not a complete remission as yet.

CASE #4

A man with carcinoma of the pancreas metastatic to the liver and with local tumor not surgically resectable developed a pancreatic

fistula through tumor tissue after treatment with thermotherapy, phloretin and chemotherapy. After one course of thermotherapy, chemotherapy, phloretin in DMSO, a marked improvement in the tumor status occurred. The pancreatic fistula through malignant tissue healed (this has never been demonstrated before) and the patient is showing steady improvement with tumor regression.

CASE #5

A man with adenocarcinoma of the lung metastatic to the lymph nodes not previously treated but demonstrated to be not surgically resectable was treated with chemotherapy, thermotherapy and phloretin in 5% DMSO. On assessment four weeks later the adenocarcinoma of the lung (considered to be a nonresponsive tumor) had decreased in size by over 50%. Further treatment is in progress.

CASE #6

A female with cancer of the breast metastatic to the bone treated previously with hormone blocking agents, chemotherapy and subsequently hyperthermia, chemotherapy and phlorizin and phloretin was maintained in a stable position but still with multiple metastases demonstrable to the skull. After three courses of treatment with combination hyperthermia and phloretin in 5% DMSO there was marked regression of the tumor in the skull with total relief of symptoms and improvement in clinical status.

CASE #7

A male with cancer of the embryonic bladder remnant with diffuse intra-abdominal metastases treated for 1.5 years with hyperthermia, chemotherapy and phlorizin developed further disease progression as demonstrated by computerized tomographic scanning of the abdomen and clinical symptoms. He

was treated with a combination of thermotherapy, chemotherapy and phlorizin in DMSO. After one month of treatment there was marked regression of tumor as demonstrated by computerized tomographic radiography of tumor in the abdomen.

CASE #8

A female with cancer of the stomach-linitus plastica type was operated on and found to have perforated through the tumor into the abdomen with diffuse tumor throughout the abdomen. There was local resection in the area of the stomach and the patient was referred for further therapy. She was treated with one course of thermotherapy, chemotherapy and phloretin in 5% DMSO. On computerized tomographic scanning of the abdomen four weeks later there was greater than 50% regression of the disease with restoration of normal gastrointestinal passage. After a second course of treatment there was complete regression of the disease.

CASE #9

A patient with malignant glioblastoma present in the left frontal lobe found not to be operable was referred for therapy and treated with hyperthermia, phlorizin, phloretin and chemotherapy. There was substantial but incomplete regression of the tumor after three courses of treatment. He was treated with one additional course of thermotherapy, chemotherapy and phloretin in 5% DMSO with marked further regression of the tumor.

For comparison purposes, in the period of February-March, 1988, I treated in excess of 250 patients in Canada with agent (a) and hyperthermia treatment (in some cases with other modalities). These patients were considered to be at the end stage. Of those treated, 15% died before the end of March, 1988.

In the period April-May, 1988, I treated 185 patients in

accordance with the teachings of my invention. Only 4.5% of the patients died. In both periods the cancer from which the patients were suffering was of the same types and the patients had been referred to me believing they were terminal. I can only account for the significant difference with the conclusion that my invention was the cause of the substantial difference in the number of deaths.

It appears that in all of the different neoplastic situations treated, although there may have been some response with the drugs that block glucose uptake in conjunction with thermal and chemotherapy there is a much greater and accelerated response when the glucose blocking drugs are given in conjunction with transport facilitating molecules. Indeed, in some instances the response has been so rapid that a reduced treatment schedule was necessary to prevent excessively rapid tumor necrosis and breakdown to avoid toxicity.

As many changes can be made to the various formulations employed without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. A formulation comprising in a form suitable for use for treating cancer, including a pharmaceutically acceptable carrier,

(a) a glucose inhibiting (non-toxic) amount of an agent that blocks the glucose transport protein (active transport molecule in the membrane) of a cancer cell from transporting glucose into the cell, and

(b) an effective (non-toxic) amount of an agent which

(i) enhances penetration and transport of agent (a) through tissue surrounding cellular elements of a cancer cell, generally known as scar tissue or fibrous reaction around a cancerous tumor, and

(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor.

2. The formulation of Claim 1, wherein the glucose inhibiting (non-toxic) agent that blocks the glucose transport protein of a cell from transporting glucose into the cell is selected from at least one of the following agents: phlorizin, phloretin or their analogues including phlorizin, glucuronide and 4-deoxy-phoretin-2-D-glucoside.

3. The formulation of Claim 1, wherein the agent which

(i) enhances penetration and transport of agent (a) through tissue surrounding cellular elements of a cancer cell, generally known as scar tissue or fibrous reaction around a cancerous tumor, and

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(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor

is selected from the group consisting of dimethyl sulfoxide (DMSO), and methylsulfonylmethane (MSM).

4. The formulation of Claim 2, wherein the agent which

(i) enhances penetration and transport of agent (a) through tissue surrounding cellular elements of a cancer cell, generally known as scar tissue or fibrous reaction around a cancerous tumor, and

(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor

is selected from the group consisting of dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM).

5. A combination comprising in a form suitable for use for treating cancer:

(a) a pharmaceutically acceptable carrier,

(b) a glucose inhibiting (non-toxic) amount of an agent that blocks the glucose transport protein (active transport molecule in the membrane) of a cell from transporting glucose into the cell, and

(c) an effective (non-toxic) amount of an agent which

(i) enhances penetration and transport of agent (a) through tissue surrounding cellular elements of a cancer cell, generally known as scar tissue or fibrous reaction around a cancerous tumor, and

(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor.

6. The combination of Claim 5, wherein the agent that blocks the glucose transport protein of a cell from transporting glucose into the cell is selected from the group consisting of the following: phlorizin, phloretin or their analogues including phlorizin glucuronide, and 4-deoxy-phoretin-2-D-glucoside.

7. The combination of Claim 5, wherein the agent which

(i) enhances penetration and transport of agent (a) through tissue surrounding cellular elements of a cancer cell, generally known as scar tissue or fibrous reaction around a cancerous tumor, and

(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor

is selected from dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM).

8. The combination of Claim 6, wherein the agent which

(i) enhances penetration and transport of agent (a) through tissue surrounding cellular elements of a cancer cell, generally known as scar tissue or fibrous reaction around a cancerous tumor, and

(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor

is selected from dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM).

9. The formulation of Claim 1, 2 or 3, wherein the formulation is in a pharmaceutically acceptable carrier.

10. Use of:

(a) a glucose inhibiting (non-toxic) amount of an agent that blocks the glucose transport protein (active transport molecule in the membrane) of a cancer cell from transporting glucose into the cell, and

(b) an effective (non-toxic) amount of an agent which

(i) enhances penetration and transport of agent (a) through tissue surrounding cellular elements of a cancer cell, generally known as scar tissue or fibrous reaction around a cancerous tumor, and

(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor,

in the manufacture of a formulation suitable for treating cancer.

11. The use of Claim 10 further comprising a pharmaceutical carrier.

12. The use of Claim 10 or 11, wherein agent (a) is selected from phlorizin, phloretin or their analogues including phlorizin glucuronide, and 4-deoxy-phoretin-2-D-glucoside.

13. The use of Claim 10 or 11, wherein agent (b) is selected from dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM).

14 A formulation suitable for use for treating cancer, the formulation comprising in a pharmaceutically acceptable carrier,

(a) a glucose inhibiting amount between about 1 - 10 grams of an agent selected from the group consisting of: phloridzin, phloretin or their analogues including phloridzin, glucuronide and 4-deoxy-phoretin-2-D-glucoside and an agent having the same effect that blocks the glucose transport protein (active transport molecule in the membrane) of a cancer cell from transporting glucose into the cell, and

(b) an effective amount of about 20 - 25 grams of an agent selected from the group consisting of dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) which

(i) enhances penetration and transport of agent (a) through tissue surrounding cellular elements (cell plasma membrane) of a cancer cell, generally known as scar tissue or fibrous reaction around the cancerous tumor, and

(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor.

per 500 - 1000 ml of formulation.

15. A combination suitable for use for treating cancer, the combination comprising in a pharmaceutically acceptable carrier,

(a) a glucose inhibiting amount between about 1 - 10 grams of an agent selected from the group consisting of: phloridzin,

phloretin or their analogues including phloridzin, glucuronide and 4-deoxy-phoretin-2-D-glucoside and an agent having the same effect that blocks the glucose transport protein (active transport molecule in the membrane) of a cancer cell from transporting glucose into the cell, and

(b) an effective amount of about 20 - 25 grams of an agent selected from the group consisting of dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) which

(i) enhances penetration and transport of agent (a) through tissue surrounding cellular elements (cell plasma membrane) of a cancer cell, generally known as scar tissue or fibrous reaction around a cancerous tumor, and

(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente